

Nature's Medicines: Traditional Knowledge and Intellectual Property Management. Case Studies from the National Institutes of Health (NIH), USA

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Abstract: With the emergence and re-emergence of infectious diseases and development of multi-drug resistance, there is a dire need to find newer cures and to produce more drugs and vaccines in the pipeline. To meet these increasing demands biomedical researchers and pharmaceutical companies are combining advanced methods of drug discovery, such as combinatorial chemistry, high-throughput screening and genomics, with conventional approaches using natural products and traditional knowledge. However, such approaches require much international cooperation and understanding of international laws and conventions as well as local customs and traditions. This article reviews the forty years of cumulative experience at the National Institutes of Health (initiated by the National Cancer Institute) in natural products drug discovery. It presents (1) three major cooperative programs (2) the legal mechanisms for cooperation and (3) illustrative case studies from these programs. We hope that these discussions and our lessons learned would be helpful to others seeking to develop their own models of cooperation for the benefit of global health.

INTRODUCTION

It is common knowledge that animals (including carnivores) often feed on certain plants, grasses or berries when they are sick. Hence, it is not surprising that since the dawn of civilization humans have learned to use plants and plant-derived products as remedies for various ailments, perhaps by taking cues from animals or through trial and error, leading to the discovery of various home-made remedies. Such practices are seen in traditional cultures, often followed by village shamans or tribal medicine men. Knowledge of herbal medicine is documented from the civilizations of Mesopotamia (2900 B.C.), Egypt (1500 B.C.), China (1100 B.C.), India (1000 B.C.), Greece (300 B.C.) and Rome (100 A.D.), and from various religious texts such as the Bible [1-4]. Ancient Chinese medicine and Ayurvedic medicine of India are practiced in their home countries even today, and such traditional knowledge from the east together with those of the Greco-Romans have been passed on to the West through careful preservation by Arabs and Persians. In addition, western European monasteries preserved the traditional knowledge (such as those of the druids) from England to Germany, through the Medieval Dark Ages.

For extended time, modern western medical practice remained indifferent to traditional medicine, often discarding such practices as unscientific. Hence, the scientific literature in the west related to plant-derived natural products and their chemistry largely remained in the academic realms of natural-products chemistry, pharmacognosy, ethnobotany and cultural anthropology. Elaborate analyses of metabolic

pathways and metabolites in plants can be credited to classical plant physiologists, biochemists and organic chemists. It is through such studies that we now understand the chemical validity of several traditional herbal remedies. Examples include the antihypertensive/tranquilizer alkaloid reserpine from *Rawolfia serpentina* or snakeroot (ancient Indian Ayurvedic medicine); the cardiotoxic glycoside digitoxin from *Digitalis purpurea* (ancient Greek medicine); various physiological stimulants in the saponins and polysaccharides from the Chinese Ginseng *Panax ginseng* (ancient Chinese medicine) as well as the American Ginseng *Panax quinquefolium* (Native American medicine), and the antimalarial/antipyretic alkaloid quinine from the bark of *Cinchona officinalis* or *Cinchona ledgeriana* (traditional South American medicine). Indeed, entire plant families such as Acanthaceae and Asclepiadaceae are comprised of botanically related members of medicinal plants described in ancient Indian, Chinese or Greek medical literature.

MODERN DRUG DISCOVERY USING NATURAL PRODUCTS

A recent review [5] concluded that 60% of the anticancer drugs and 75% of the anti-infectious disease drugs approved from 1981-2002, could be traced to natural origins. In addition, 61% of all new chemical entities introduced worldwide as drugs during the same period could be traced to or were inspired by natural products.

The major categories of plant-derived compounds that have medicinal properties are the terpenoids (such as taxol and various steroids), the glycosides (such as digitalis and

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various flavonoids) and the alkaloids (such as reserpine and various opiates) [6]. A great number of naturally derived medicinally important compounds also originate from microorganisms and marine organisms [1, 7]. Examples include antibiotics such as streptomycin from the soil bacteria of the genus *Streptomyces spp.*, penicillin from the fungus *Penicillium spp.* and conotoxins (peptide neurotoxins) from the marine snails *Conus spp.* Several of today's most promising pipeline candidates in oncology, such as ecteinascidin, halichondrin, bryostatin, and the epothiolones, all arose from screening of natural products followed by synthetic modifications [1, 7].

Despite the above facts, for a number of years there had been a decline in the use of natural products as starting materials for drug discovery. The lack of interest in utilizing natural resources can be partly attributed to (1) rediscovery problems due to technical difficulties, and (2) access to natural/genetic resources and intellectual property (IP) issues while working across nations and cultures [8-11]. Technical difficulties generally arise with the characterization and purification of naturally-occurring medicinal compounds (especially when source materials were limited), difficulties with high-throughput screening (HTS), and with the laboratory-scale synthesis and commercial production of such structurally and stereochemically complex compounds in bulk quantities. Difficulties with access to genetic resources and IP are often related to resource management problems, complications related to sharing of benefits, confusion over patent rights vs. resource ownership, and difficulties with agreement structure. Many pharmaceutical companies preferred to design drugs by other scientific approaches rather than taking leads from nature after learning from experience that the success of drug discovery from plants and other organisms were few and far between, time consuming and expensive, and there was always the possibility that years of research may lead to compounds that are non-patentable and nonproprietary. The marginal returns from such projects compounded with the social, legal and technical problems, made this business less attractive to the pharmaceutical industry, which leaned more towards novel approaches such as combinatorial chemistry and "virtual" drug discovery.

However, as the need to find new cures for diseases becomes even more pressing, due to the re-emergence of infectious diseases and multi-drug resistance, there is renewed interest to find solutions from nature. Despite the promise of combinatorial chemistry the drug pipeline could undoubtedly benefit from all avenues of research, thus leading to the revival of natural products. Scientists have recognized that while it is difficult to characterize pharmaceutically important compounds from nature, it is even more difficult to conceive complex molecules with therapeutic potential from synthetic chemistry alone. For example, complex compounds such as paclitaxel (taxol) would never have been synthesized in the laboratory, if they had not been identified initially from nature and discovered to contain anti-cancer properties. Hence, the structural and functional diversity and the biochemical specificity obtained in natural products offers possibilities unmatched by synthetic compounds [9]. Metabolic studies of plant-derived pharmaceuticals help to understand structure-activity

relationships between drugs and their cellular targets, and also help to design more effective novel drugs by chemical synthesis. Such second-generation chemicals may be synthesized to mimic naturally occurring compounds but with greater specificity and less toxicity. A detailed review of the metabolism of common plant-derived anticancer agents has been provided by the National Cancer Institute (NCI), the largest of the institutes of the U.S. National Institutes of Health (NIH) [12]. The diversity of chemical structures available from natural sources offers higher probability of pharmaceutical leads and hence, it is no surprise that >60% of currently available drugs (including several major blockbuster drugs) originate from natural products, as discussed earlier. In fact, nearly half of the 200 most widely-prescribed drugs in the U.S. are natural products or derivatives [9]. Use of natural products as templates helps to generate simpler analogs with better activity and absorption, distribution, metabolism and excretion (ADME) characteristics. Combining traditional approaches to drug discovery with advanced methods involving combinatorial chemistry, HTS and plant genomics, enhances the probability of success for the pharmaceutical industry, which is now prepared for "molecular pharming" of plant-derived biochemicals [9].

Given the benefits of utilizing natural resources as starting materials of drug development and the renewed interest of the research community, the socio-political and legal hurdles encountered in international cooperation need to be understood and the difficulties need to be resolved. In the next section we analyze some of the challenges that can hinder drug discovery.

CHALLENGES OF INTERNATIONAL COLLABORATION INVOLVING DRUG DISCOVERY FROM NATURAL PRODUCTS

There are various hurdles to cross while working with natural products from other countries, particularly developing countries. In the simplest scenario, such work may involve utilization of natural genetic resources from a source country. Issues surrounding use of genetic resources include conservation of local biological diversity and protection of species that may be endangered, sustainable use of these resources for the economic benefit of local communities, and equitable benefit sharing. Even more complex are the issues surrounding sharing of traditional knowledge regarding the medicinal value of a particular natural resource. These involve issues regarding sharing of traditional know-how, national and international laws pertaining to intellectual property, informed consent, etc. Indeed, sharing of traditional knowledge and indigenous biological/genetic resources is a challenge mired in controversies emerging from history of colonial exploitation in the developing world, local politics, and the global policies and guidelines established via international instruments such as the United Nations Convention on Biological Diversity (CBD) and the Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) of the World Trade Organization (WTO) [10, 11]. The controversies involve appropriate valuation of traditional knowledge and natural resources and accurate determination of ownership of intellectual property. For example, from the

perspective of the developing world, how can one be sure that after a multinational company has found a profit-making compound, it will not find the means to synthesize it in the laboratory, thus eliminating sharing of profits with its partners who contributed traditional knowledge and local genetic resources? Since traditional knowledge is generally in the public domain and therefore not patentable, how can local people be compensated for their traditional knowledge? From the perspective of a company, what is the guarantee that it will receive from the source country an uninterrupted supply of materials during research and development (R&D) as well as large-scale manufacturing of a potential therapeutic? Does the country have the resources and capacity necessary for the development and scale-up of novel synthetic methodologies and also for "farming" or harvesting of the natural product in its native form? Moreover, which person/entity in the source country has the rightful authority to provide informed consent – is it the national/state/local government, a local non-governmental organization (NGO) representing the communities, the community/tribal leader, or the individual(s) who have the knowledge of the source and its medicinal value? Numerous questions remain to be answered.

While these questions are not always easy to answer, the scientific community can benefit from the lessons learned by other researchers involved in collaboration across national boundaries. In the following pages, we provide an account of the major NIH programs for international cooperation in drug discovery involving natural products. We also describe the cooperative methods employed, through a selection of case studies from NIH, which may be useful models for international collaboration involving equitable sharing of IP and natural resources.

Major Cooperative Programs and Mechanisms for Drug Discovery / Development Research at NIH

These programs include:

- I. The NCI-Developmental Therapeutics Program (DTP);
- II. The NCI-National Cooperative Drug Discovery Group (NCDDG);
- III. The International Cooperative Biodiversity Groups (ICBGs), administered by the Fogarty International Center (FIC).

Through these programs, several cooperative mechanisms have been established to promote equitable sharing of benefits and conservation of natural resources. The mechanisms are:

Letter of Collection (LOC), NCI

Memorandum of Understanding (MOU), NCI

Specific Material Transfer Agreements (MTAs), used for the exchange of materials with outside organizations for research purposes.

Details of individual Programs and Mechanisms are provided at the websites and in the references listed in Table 1.

A. NIH COOPERATIVE PROGRAMS FOR DRUG DEVELOPMENT USING NATURAL PRODUCTS

PROGRAM I. DEVELOPMENTAL THERAPEUTICS PROGRAM (DTP)

This is the earliest among NCI's cooperative programs, within the Division of Cancer Treatment & Diagnosis (DCTD). First designed for the preclinical development of therapeutics for cancer (1960s), the Developmental Therapeutics Program (DTP) was later expanded to include drug discovery for HIV/AIDS (1988), although the anti-HIV screening activity was subsequently discontinued. Agents showing promise in animal models during the preclinical phase of drug development through DTP, are further tested in humans at the clinical phase of drug development through a separate program within DCTD, known as the Clinical Trials Evaluation Program (CTEP).

Table 1.

<p>NIH Cooperative Programs for Drug Development</p> <p>Developmental Therapeutics Program (DTP), Division of Cancer Treatment & Diagnosis (DCTD), NCI [1, 2, 13] http://dtp.nci.nih.gov/</p> <p>NCI DTP Natural Products Branch & NCI Natural Products Repository http://dtp.nci.nih.gov/branches/npb/index.html</p> <p>National Cooperative Drug Discovery Group (NCDDG) [7, 14] http://dtp.nci.nih.gov/branches/gcob/gcob_web3.html</p> <p>International Cooperative Biodiversity Groups (ICBG) [15-20] http://www.fic.nih.gov/programs/icbg.html</p> <p>NCI Cooperative Mechanisms for Drug Development</p> <p>Letter of Collection (LOC), NCI http://ttb.nci.nih.gov/nploc.html</p> <p>Memorandum of Understanding (MOU), NCI http://ttb.nci.nih.gov/npmou.html</p> <p>Material Transfer Agreements (MTA), NCI http://ttb.nci.nih.gov/slafaq.html</p> <p>Cooperative Research And Development Agreements (CRADA), NIH http://ott.od.nih.gov/model_agree.html</p>
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Table 2.

<p>Drug Discovery and Development using Natural Products at NCI, Division of Cancer Treatment & Diagnosis (DCTD) http://cancer.gov/dctd/</p> <p><u>Developmental Therapeutics Program (DTP), DCTD</u> http://dtp.nci.nih.gov/</p> <p>Step 1: Plant Collection. NCI Plant <u>Acquisition</u> Program [LOC/MOU] Step 2: Natural Product Drug Discovery Program: drug screening, isolation and structural elucidation Step 3: Drug Development Program [CRADA; Licensing Agreements] ⇒ Preclinical Development</p> <ol style="list-style-type: none"> 1. Large-Scale Production of Natural Products: large-scale synthesis and economic production 2. Analog Development: Structure-Activity Relationships (SAR) etc 3. Formulation: drug vehicle studies 4. Pharmacological Evaluation: animal studies, pharmacokinetics, metabolism studies 5. Toxicological Evaluation: rodent and dog models <p><u>Clinical Trials Evaluation Program (CTEP), DCTD</u> http://ctep.cancer.gov/</p> <p>⇒ Clinical Development: IND filing with FDA; Phase I, II, III Trials in humans; NDA filing with FDA</p>	
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Designed for NIH intramural research, DTP includes the *Natural Products Therapeutics Program* involving development of therapeutics from natural resources. The DTP has an Acquisition Program for plant, microbial and marine resources from various geographical regions. Samples are collected by region-specific contract collectors within the source country according to the terms outlined in a standard Letter of Collection (LOC). NCI also receives materials directly from research collaborators in source countries. Such materials are received according to terms outlined in a Memorandum of Understanding (MOU).

The Natural Products Branch (NPB) of NCI's DCTD is responsible for coordinating programs directed at the discovery and development of novel, naturally derived agents to treat cancer. Specifically, the NPB is responsible for:

- [1] Acquiring crude biological materials of plant, marine and microbial origin for NCI's drug screening programs.
- [2] Coordinating research directed towards isolation of new agents.
- [3] Assisting in large-scale production of new agents for preclinical and clinical development.

The NPB has specific policies for international collaboration and compensation, as indicated in the LOC or MOU. In recent years, NCI is leaning more towards collaborative programs (as exemplified in the MOU) with source countries, where scientists are actively engaged in the drug discovery and development process, and less towards utilization of contract collectors. Utilizing the MOU, NCI has established collaborations with organizations in Australia, Bangladesh, Brazil, China, Costa Rica, Fiji, Iceland, Korea, Mexico, New Zealand, Nicaragua, Pakistan, Panama, Papua New Guinea, South Africa, and Zimbabwe. Resources deposited in the Natural Products Repository (NPR) follow a standard path to drug discovery, discussed later in this section.

Biological materials acquired by NPB through LOC or MOU are deposited in NCI's NPR, which has a collection of over 60,000 specimens. Researchers outside NIH can

procure from the NPR the materials that were obtained through a LOC, by signing of a legally binding NPR-Material Transfer Agreement (NPR-MTA). As indicated in the MTA, all resource recipients must honor the terms of the LOC under which the natural resources were initially procured. Compounds/extracts obtained directly from source-country research collaborators through MOU are always classified as 'discrete' and are not distributed outside NIH. As stated in Article 18 of the standard MOU, "*DTP/NCI will not distribute materials provided by [SCO] to other organizations without written authorization from [SCO]. However, should [SCO] wish to consider collaboration with organizations selected by NCI for distribution of materials acquired through NCI collection contracts, DTP/NCI will establish contact between such organizations and [SCO].*"

Drug Discovery Process at NCI Involving Natural Products

The path to drug discovery, starting from natural samples – plants, animals, microbes, marine organisms – follows a sequential course. The steps involved in this process are outlined below (see Table 2).

Drug Discovery Phase - Extracts of biological samples deposited in the NPR undergo screening in cellular and animal models for biological effects; extracts showing positive results in initial screening are subjected to bio-assay-directed fractionation and further testing leading to the isolation and structural characterization of active compound(s).

Preclinical Drug Development – Structure-activity relationships involving chemical modifications that may enhance biological activity and bioavailability while minimizing toxicity. At this stage, a researcher may seek the assistance of biotech or pharmaceutical companies for complex processes involved in drug development. Such partnership between NIH researchers and the industry often occurs *via* Cooperative Research And Development Agreements (CRADAs) (see Table 1). The terms of the CRADA must be consistent with the principles of LOC or MOU. Specific clauses IN CRADAs are included regarding

handling of IP, such as filing of patents and licensing, should any IP be generated in the collaboration.

Clinical Development – Compounds that show promise in all preliminary tests and in animal models are then clinically tested in humans through CTEP. This involves filing of an Investigational New Drug Application (INDA) with the US Food & Drug Administration (FDA), running Phase I, II & III Clinical Trials for maximum tolerated dose, and finally submitting a New Drug Application (NDA) with FDA.

PROGRAM II. NATIONAL COOPERATIVE DRUG DISCOVERY GROUP (NCDDG)

The NCDDG was established by NCI in 1983 to fund all aspects of preclinical anticancer drug discovery and treatment strategies utilizing either synthetic sources or natural products (*National Cooperative Natural Products Drug Discovery Group or NCNPDDG*). As compared to the DTP, this program has a further level of complexity in that it takes a multi-institutional and multi-disciplinary approach to drug discovery. The NCDDG funds research consortia initiated by extramural investigators i.e., investigators who are recipients of NIH grants but work outside NIH, such as at universities. NCDDG programs demonstrate effective partnerships between the government (NCI), academia and industry with the goal of drug discovery, and there is much cross-fertilization of ideas and resources amongst the collaborating partners within each group. Groups utilizing natural products generally contain several university partners (one of which is the lead institution) and one industrial partner. The collaborating members within a group are funded as cooperative agreements in response to a Request for Applications (RFA). Although legally an assistance mechanism, like a grant, this mechanism is unlike other NIH grant mechanisms in that NCI is directly involved with the conduct of activities of the research partners within the cooperative groups that receive funding from NCI through NCI representatives. Members of NCDDG use the same guiding principles of DTP and honor the principles outlined in the NCI LOC/MOU. Since its inception, over the past 20 years (1983-2003), NCDDG has made several rounds of competitive awards, with a total of 42 awards and renewal of funding for 16 groups. Hundreds of thousands of natural-product extracts have been tested and some agents discovered are now undergoing preclinical or clinical development. Investigative, natural products-based anticancer agents that have emerged from NCDDG programs and are in advanced stage of clinical trial or have gained FDA approval include topotecan (a semi-synthetic derivative of a plant alkaloid camptothecin), cryptophycin from a cyanobacterium (or blue-green alga), and HTI 286 and LAF389 (analogs of natural compounds) from marine sponges (see Case Study 2). A detailed review of the projects emerging from NCDDG has been published [7].

PROGRAM III. INTERNATIONAL COOPERATIVE BIODIVERSITY GROUPS (ICBG)

The founding principles of ICBG's were conceived at an international workshop on drug development, biodiversity conservation and economic growth in 1991 and the first RFA

for this program was released in 1992. Based on the structural model of the NCI-NCDDG, the ICBG has several layers of complexity:

(1) In addition to drug discovery and development from natural products (as in the case of NCDDG), this program includes goals for conservation of biological diversity and economic development of source countries.

(2) Because it includes additional components beyond drug discovery, such as conservation of genetic resources, agriculture and sustainable development, this program involves other agencies of the U.S. Government beside NIH as funding partners. In 1992, the initial partners were NIH, the National Science Foundation (NSF) and the U.S. Agency for International Development (USAID); in 1997 during the second round of RFA, the Foreign Agricultural Service (FAS) of the U.S. Department of Agriculture (USDA) joined the program while USAID left in 1995 due to budgetary constraints.

(3) Administered by the Fogarty International Center (FIC) of NIH, the program involves other participating Institutes in addition to NCI – the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Drug Abuse (NIDA), the National Institute of Mental Health (NIMH) and the National Heart, Lung and Blood Institute (NHLBI).

(4) ICBG involves several cooperative groups of research partners (universities, foundations and private enterprises/industries) within the U.S. working with foreign counterparts.

ICBG Structure

Each ICBG is a consortium of several Associate Programs under the leadership of one Principal Investigator or Group Leader – all functioning as a single unit with a common goal to promote drug development, biodiversity conservation and economic development through multidisciplinary approaches. Each Associate Program functions as a unique component of the Group with a unique resource, capability or expertise and at least one of these programs must be located in a developing country with significant biological diversity. Public and private non-profit institutions, for-profit institutions, Governments and their agencies, and foreign institutions are eligible to participate as members of a Cooperative Group. Foreign and for-profit institutions may participate as Associate Programs of an ICBG, being managed by Associate Program Leaders. The Group Leader of an ICBG, who is the Principal Investigator for the grant, coordinates all Associate Programs and must be located in a public or private non-profit institution, or Government /Government Agency of the U.S. Each ICBG is advised by a Technical Advisory Group (TAG) – a committee of experts from participating Agencies and Institutes. The TAG also includes the FIC Biodiversity Program Director who serves as the Government administrator of all ICBGs funded and U.S. Government Scientific Coordinators, each assisting a particular ICBG. The funding mechanism is through Cooperative Agreements between the U.S. Government and each ICBG, rather than through Grant awards. Such Agreements allow the

Table 3.

International Cooperative Biodiversity Groups (ICBG) programs:	
<u>Objectives</u>	
1.	Improve human health through discovery of natural products with medicinal properties
2.	Conserve biodiversity through valuation of natural resources, training and infrastructure building to aid in management
3.	Promote sustainable economic activity of communities, primarily in less developed countries in which much of world's biodiversity is found.
<u>Principles</u>	
1.	Disclosure to and informed consent of host country stakeholders
2.	Clear designation of the rights and responsibilities of all partners
3.	Protection of inventions using patents or other legal mechanisms
4.	Sharing of benefits with the appropriate source country parties
5.	Information flow that balances proprietary, collaborative and public needs
6.	Respect for and compliance with relevant national and international laws, conventions and other standards.

sponsoring Government components to exercise substantial programmatic involvement to achieve goals and objectives of the project even though there is no intent (real or implied) for Government staff to direct or restrict a Group activity. The total budget of the ICBG program is currently little over \$5 million (FY 2005). The program has completed two 5-year cycles with eight (8) cooperative groups being funded over the first (1993-94) and second (1997) round of awards. These projects have been described in detail in a special publication [19]. A third round of awards is in mid cycle, including 4 new groups. Although the eight cooperative groups have diverse approaches to their projects and include 35 organizations in 12 countries spanning four continents they all attempt to meet the same objectives and abide by the same principles outlined in Table 3.

B. LEGAL MECHANISMS FOR INTERNATIONAL COOPERATION IN DRUG DEVELOPMENT USING NATURAL PRODUCTS

In the previous section we have discussed how various programs for drug development using natural products evolved at NIH. The NCI DTP model paved the way for the NCDDGs, which in turn provided the structural basis for the ICBGs administered by FIC. Thus, the principles enumerated in the NCI DTP's LOC and MOU, provide the fundamental framework for international cooperation in all NIH Programs for drug development using natural products. The standard LOU and MOU are available at the websites provided in Table 1.

When dealing with traditional knowledge and genetic resources, it is to be noted that these assets cannot be assessed by the same criteria as those applied for other kinds of assets. For example, traditional knowledge generally belongs to a community and therefore, lies in the public domain. Hence, it does not meet the standard criteria of novelty, utility and non-obviousness, as applied to inventions by the U.S. Patent law, and does not warrant intellectual property protection. Also, while most western countries share similar patent laws that define inventorship, there are specific differences in the laws from one country to another and they are applicable only within the boundaries of each country. Moreover, there are specific patent laws pertaining to plant material, which can vary considerably between nations [21]. Hence, in international collaborations involving

traditional knowledge and/or genetic resources, structured benefit-sharing agreements negotiated upfront may help to transcend national barriers and assist cooperating parties to reach clearly defined common understanding. Agreements may incorporate plans for benefit sharing in the form of royalties (upfront royalties and/or royalties decided only after product shows promise), milestone payments and intangible gains of capacity building via local training and infrastructure development. For NIH, the NCI LOC and MOU have helped to address these issues and to establish some ground rules while embarking on such collaborations.

NCI LOC and MOU

The LOC and the MOU developed at NCI recognize the value of the natural resources (plant, marine, microbial) being investigated by the NCI researchers, and the significant contributions being made by the source country (SC), source country government (SCG), or source country organization (SCO) in aiding the NCI collection programs. Hence, these agreements attempt to balance the interests of the indigenous peoples, SC and SCO, with those of the U.S. Government and private sectors. Several policies, aimed at facilitating collaboration with and compensation of countries participating in the NCI drug discovery program, have been developed. These policies, which were initially outlined in the NCI/DTP Letter of Intent (LOI) [2], have later been implemented through the LOC and MOU. They are also included in the form of public policy or public benefit obligations (so called "White Knight" clauses) in licensing agreements developed at the NIH Office of Technology Transfer (OTT).

It must be mentioned at the onset that the NCI LOC and MOU are not mechanisms for licensing IP Rights (IPR) in cooperative research funded by the U.S. Government. Such rights can only be delineated in a CRADA by U.S. law [discussed in detail in Ref. 2]. Generally, a CRADA is only negotiated at a stage of research when there is a defined invention that needs further development with the assistance of a commercial partner. The policy of NIH is to defer negotiations regarding licensing of IPR and specific royalty rates until a specific invention is identified. Therefore, at early stages of drug discovery involving natural products, when the results are uncertain, no commitments regarding IP (involving patenting or licensing) can be made by NIH, an

Agency of the U.S. Government. However, these same internal policies dictate NCI to "make best effort" (a phrase of specific significance in U.S. law, implying strong commitment) in providing opportunities to its collaborating partners for continuous engagement in the drug discovery process and fair and equitable compensation, where applicable.

For example, NCI/DTP policy dictates that if drug is commercialized, the SCO is appropriately compensated. As stated in Article 8 of the LOC, *"Should an agent derived from an organism collected under the terms of this agreement eventually be licensed to a pharmaceutical company for production and marketing, DTP/NCI, will request that NIH/OTT require the successful licensee to negotiate and enter into agreement(s) with appropriate [SCG] agency(ies) or [SCO] within twelve (12) months from the execution of said license. This agreement(s) will address the concern on the part of the [SCG or SCO] that pertinent agencies, institutions and/or persons receive royalties and other forms of compensation, as appropriate."* The above benefits are provided regardless of whether the development is for a direct isolate or synthetic material derivative. As stated in Article 9 of LOC - *"The terms of Article 8 shall apply equally to inventions directed to a direct isolate from a natural product material, a product structurally based upon an isolate from the natural product material, a synthetic material for which the natural product material provided a key development lead, or a method of synthesis or use of any aforementioned isolate, product or material; though the percentage of royalties negotiated as payment might vary depending upon the relationship of the marketed drug to the originally isolated product. It is understood that the eventual development of a drug to the stage of marketing is a long term process which may require 10-15 years."*

Also, collection contractors must collaborate with SCO through the duration of the project. To ensure continued involvement of the SC/SCO, the drug developer must use the SC as first source of bulk natural product supply if possible. According to Article 10 of LOC, *"In obtaining licensees, the DTP/NCI/NIH will require the license applicant to seek as its first source of supply the natural products from [Source Country]. If no appropriate licensee is found that will use natural products available from [Source Country], or if the [SCG] or [SCO] as appropriate, or its suppliers cannot provide adequate amounts of raw materials at a mutually agreeable fair price, the licensee will be required to pay the [SCG] or [SCO] as appropriate, compensation (to be negotiated) to be used for expenses associated with cultivation of medicinal organisms that are endangered, or for other appropriate conservation measures. These terms will also apply in the event that the licensee begins to market a synthetic material for which a material from [Source Country] provided a key development lead."*

With the increasing awareness of the value of indigenous genetic resources, many countries now prefer to carry out initial research in the home country. For this reason, NCI now favors the use of the MOU with collaborating SCOs that are suitably qualified to perform in-country processing rather than using contract collectors and LOC. NCI assists the SCO in establishing a pre-screen and active SCO extracts or

compounds are perhaps further screened at NCI. Joint patents are sought on all inventions co-developed under the MOU between SCO and DTP. SCOs can also be sole inventors. As stated in Article 9 of MOU, *"Both [SCO] and DTP/NCI recognize that inventorship will be determined under patent law. DTP/NCI/NIH and [SCO] will, as appropriate, jointly seek patent protection on all inventions jointly developed under this MOU by DTP/NCI and [SCO] employees, and will seek appropriate protection abroad, including in [Source Country], if appropriate. Application for patent protection on inventions made by [SCO] employees alone will be the responsibility of [SCO]. Application for patent protection on inventions made by DTP/NCI employees alone will be the responsibility of DTP/NCI."*

When materials are collected under the LOC, NCI/DTP takes the lead in isolating, characterizing, and patenting active agents. However, a major component of NCI/DTP is also to promote development of the agent in the SC. Therefore, capacity building plays an important role in the process. The agreements enable SC scientists to work at NCI as guest researchers whenever possible, and training is provided for SCO scientists. DTP/NCI also provides a number of resources to the SC/SCO free of charge, without claiming contribution toward inventorship in drug development. Some examples include (1) *in vitro* screening of natural product extracts and compounds, (2) *in vivo* evaluation of efficacy, and (3) algorithms for possibly identifying anti-tumor compounds with new mechanisms of action. Such "soft benefits" may sometimes be of greater value to the SC/SCO over the long term than financial payments. This is especially true when the research may not eventually lead to any product development due to failure in clinical trials, technical difficulties, etc. According to Article 3 of the LOC, *"in the course of the contract period, DTP/NCI will assist the [SCO], thereby assisting [SC], to develop the capacity to undertake drug discovery and development, including capabilities for the screening and isolation of active compounds from plants, micro-organisms and marine organisms."* Similar language is also provided in Article 6 of MOU. The LOC goes further to state: *"Subject to the provision that suitable laboratory space and other necessary resources are available, DTP/NCI agrees to invite a senior technician or scientist designated by [SCO] to work in the laboratories of DTP/NCI or, if the parties agree, in laboratories using technology which would be useful in furthering work under this agreement"* [Article 4].... *"The DTP/NCI will make a sincere effort to transfer any knowledge, expertise, and technology developed during such collaboration in the discovery and development process to [SCO], subject to the provision of mutually acceptable guarantees for the protection of intellectual property associated with any patented technology"* [Article 5]. The above clauses are also iterated in the MOU, in Articles 7 and 10, respectively.

Both the LOC and the MOU also contain elaborate guidelines for the process of data sharing and mutual confidentiality between NCI and SC/SCO, for the purpose of IP protection and technology development. MOUs are generally five-year agreements, while the LOCs have no expiration date. For the benefit of the provider, NCI

Table 4.

Guiding principles of benefit-sharing agreements in NCI/NIH-funded programs involving natural products for drug development:	
If a drug is developed and commercialized, utilizing natural products from source countries, then	
1.	NIH requires that the SC or SCO receive royalties and other appropriate forms of compensation.
2.	Royalties depend upon the relationship of the marketed drug to the original lead from the extract (e.g., the structural relationship between the commercialized drug moiety and the lead compound as originally isolated) and the scientific contribution to the invention by SCO.
3.	Licensee must initiate negotiations with the SC/SCO by the start of clinical trials and compensate them by commercialization/sale of drug.
4.	Licensee is encouraged to begin and complete negotiations typically within one year of signing the licensing agreement.

expresses its desire to adhere to all the terms of the LOC or MOU, even in absence of a formal agreement or when the MOU has expired.

The principles of benefit sharing outlined in the NCDDG and the ICBG utilize the model of NCI DTP and the overarching elements of the NCI LOC/MOU agreements provide a foundation for these extramural programs. As discussed earlier, both NCDDG and ICBG programs are initiated by U.S. investigators outside NIH that receive NIH funding; however, NIH has considerable involvement in these programs to achieve the desired goals and objectives. The guiding principles of benefit sharing agreements for all three programs – NCI/DTP, NCDDG and ICBG – are itemized in Table 4.

Article 15.1 of the CBD recognizes the rights of national governments to regulate access to genetic resources located within their borders. Article 15.5 specifies the requirement of prior informed consent (PIC) from the party that provides access to its genetic resources. Article 8(j) of the CBD recognizes the rights of indigenous and local communities on their traditional knowledge, innovation and practices [22,11]. It is noteworthy that the NCI LOC was drafted in 1988 - 4 years prior to the drafting of the CBD (1992) by the UN. Yet, the LOC (and the MOU, drafted shortly thereafter) contain the same ideals and policies as the CBD regarding equitable benefit sharing between the U.S. and the developing source countries, and for capacity building of SCs with the purpose of technological and economic development. The DTP also paid attention to the ecological value of natural resources and promoted their sustainable use.

The above philosophy and associated policies were also adopted in the ICBG Program, later developed by FIC. Although the U.S. did not become a signatory to the CBD, which was adopted at the "Earth Summit" in Rio de Janeiro in 1992, the underlying principles of the CBD – conservation, sustainable use and equitable benefit sharing – are the same as those of the ICBG program funded through the U.S. Government. The ICBG program attempts to meet the same three goals through research and development in a manner compatible with existing legal frameworks such as the CBD and TRIPS. Operationally, the ICBG program has served to provide a functional model for some countries party to the CBD. Developing countries participating in ICBG have used the mechanism as a testing ground for creating public-private partnerships and developing policies

relevant to CBD, such as access and benefit sharing for genetic resources.

Mechanisms Specific to ICBG

The terms and conditions of equitable benefit sharing in ICBG agreements have been published in detail and will not be discussed here [Rosenthal, JP "Equitable Sharing of Biodiversity Benefits: Agreements on Genetic Resources" presented at International Conference on Incentive Measures for the Conservation and Sustainable Use of Biological Diversity, Cairns, Australia, 25-28 March 1996]. However, we highlight below some unique issues and elements of legal mechanisms specifically encountered in agreements within certain ICBG programs, which vary from the DTP mechanisms [17].

I. Royalty Structure:

Royalties are usually percentages of the selling price of commercialized products. For all cooperative programs discussed above, monetary compensation in the form of royalties, as negotiated in a contract, depends on the relative contribution of collaborating partners. The valuation of the royalty may depend on the chemical nature of the pharmaceutical product (e.g., the structural relationship between the commercialized drug moiety and the lead compound as originally isolated) or the kinds of assays (functional vs. mechanistic) by which the active principle was detected. For example, a higher royalty is generally obtained if the commercialized product is a direct isolate or very similar to the source natural product rather than a chemically-modified derivative of the original compound or structural moiety found in the extract. In addition to the above, for certain ICBG programs, the timing of the negotiations has also been known to influence royalty structure. Unlike in NCI/DTP, where negotiations regarding licensing of IPR and specific royalty rates are deferred until positive results for natural products are obtained on NCI screens or a specific invention is determined, ICBG benefit-sharing negotiations have been known to occur either before or after positive drug-screening data were conclusively obtained. Usually the SC or SCO negotiates a higher rate of royalty when positive results exist from the screening of extracts. On the other hand, in the absence of screening data, the SC or SCO may still negotiate upfront payments at the onset of collaboration to assure some monetary gain regardless of the outcome. However, the negotiated rates of such upfront royalties are always less because of the

uncertainty of the outcome. Hence, this is a low-risk, low-return form of partnership investment for SC/SCO.

II. Know-How Licenses:

Compared to genetic resources, even more difficult is the process of valuation and compensation of traditional knowledge that might play an integral part in drug development. Traditional ethno-botanical knowledge may help researchers to identify what part of a plant contains the active medicinal moiety, what times of the year are best for harvesting the material and so on. A given compound may be concentrated in the roots rather than in the aerial systems of a plant and may appear to be synthesized in a particular season or developmental stage of the plant. Traditional ethno-medical knowledge may provide direct association between a natural product (e.g., plant extract) and its use as remedy against a type of disease. Obtaining such indigenous knowledge may greatly expedite the process of drug discovery and reduce the costs in terms of time, labor and utilization of research resources (such as by reducing the number of expensive assays that need to be performed). It can also make drug discovery from natural products cost-effective (1) by efficacious short-listing of pharmacologically-active plants etc., and (2) by providing a specific end use for the product [23]. For example, the anti-HIV moiety found in the bark of *Homalanthus nutans*, a tree growing in the rain forests of Western Samoa, occurs in one of two varieties and is produced only when the tree is of a certain size. Dr. Paul Alan Cox, an American ethnobotanist, obtained this pertinent information from local Samoans who used this tree bark for centuries for treatment against symptoms of liver diseases resembling those of yellow fever and hepatitis, and this traditional knowledge guided his discovery of prostratin (see Case Study 3).

It is important to remember, however, that because of its existence in the public domain, traditional knowledge is non-patentable. Compensation for such knowledge may be through various forms of agreement structure. One such mechanism is the use of a "know-how license" - a type of industrial agreement that provides the licensee exclusive or non-exclusive rights to utilize the informal knowledge for associated technology development. While not always easy to negotiate due to legal complications, such a mechanism has been used in some ICBG programs to provide financial compensation for the use of such knowledge. A know-how license helps to recognize and protect indigenous knowledge in a manner that is commercially viable and resonant with the procedures of the industries in the developed world.

III. Issues involving Ownership of Genetic Resources and Traditional Knowledge:

The ICBG Program requires that near- and long-term benefits be returned to collaborating communities, whether it is solely for the utilization of genetic resources or for both the resources and traditional knowledge associated with such resources. Genetic resources of natural products are generally owned by the SCG or local owners of the land. The CBD recognizes the sovereignty of nations over their genetic resources (Article 15). Hence, these are the benefit-sharing entities of the partnership with respect to resources.

However, it is a daunting task to identify who is the rightful owner of traditional knowledge, especially when that knowledge has been around for generations. Legal owners to traditional knowledge may be the individual, the community, the local/state/national government and even non-governmental organizations that represent the indigenous people [20]. Furthermore, communities may be defined by geographic boundaries, ethnicity or political divide. The challenge of identifying ownership and benefit recipients due to such ambiguity can lead to major legal complications in negotiations involving know-how licenses (discussed in the previous segment) and in the identification of local authority to provide PIC (discussed at the end of this essay).

IV. Negotiations and Forms of Agreement Structure

In the ICBG, program leaders of the cooperative groups generally lay out the basic principles of the agreements, which are then reviewed by associate programs within each group. Since scientists, conservation workers or government representatives often do not have the legal competence or experience to evaluate terms of agreements (unlike industrial partners), they are highly encouraged to utilize legal counsel to analyze the potential pitfalls and provide advice on the draft agreement early on, prior to the commencement of the research project. Given that all circumstances cannot be anticipated in advance, negotiations may continue throughout the progress of the project and agreements may be modified accordingly. Negotiated issues include ownership and conditions of material transfer, patent rights, types of benefits and benefit recipients. As part of an agreement, full disclosure of research objectives and PIC from source-country participants is also emphasized and these often require clear communication and intense negotiations.

Various forms of Agreement Structure have been encountered in various ICBGs. At the primary level each ICBG begins with a cooperative agreement between the U.S. Government (USG) and the principal investigator or program leader of the ICBG at a U.S. university. Funding from the USG is contingent upon the fulfillment of ICBG principles and satisfactory progress on the part of the groups as well as availability of funds in the USG. Agreements have been drawn on the basis of simple "one-contract" model or highly complex "wheel-of-contracts" model and everything in between. In the one-contract model, all participating associate programs have a single multilateral contract agreement with the lead investigator, who in turn has a legal agreement with the USG. While this is the simplest of all agreement structures, it is the most difficult and time-consuming to negotiate, as all parties need to come to agreement on all terms as partners. In the wheel-of-contracts model, which represents an extreme scenario, participating associate programs have bilateral agreements with each other and with the lead program. Such bilateral agreements are simpler to negotiate and do not affect the entire group all at once. However, this structure requires efficient management on part of the lead program that acts as the "hub." A third model is the "dual-contract model" in which the collections and benefit-sharing agreement is separate from the commercial research and development agreement and participating associate programs may be signatories to either

one or the other or both, hence exhibiting an overlapping structure. This arrangement helps to separate the aspects of resource and knowledge utilization, which are culturally and politically sensitive issues, from the aspects of commercial research and development.

All the salient points discussed above have been encountered in at least one or more ICBGs.

We end this discussion by providing three examples of R&D cooperation for drug development from Natural Products.

CASE STUDIES

1. THE CALANOLIDES - POTENTIAL ANTI-HIV AGENTS FROM MALAYSIAN RAIN FORESTS

NIH Program – NCI/DTP

Consortium Goal

To discover anti-cancer and anti-HIV agents from natural products

Consortium Members

U.S. Academic Partner(s) – University of Illinois at Chicago (UIC)

U.S. Industrial Partner(s) – Medichem Research, Inc., Illinois

International Partners(s) – Forestry Department, State Government of Sarawak, Malaysia

Genetic Resources utilized – *Calophyllum* spp. (Guttiferae); trees in a tropical rain forest of Sarawak, Malaysia

Traditional Knowledge utilized – None

In 1986 an exploration program was undertaken under NCI contracts with the University of Illinois at Chicago (UIC) for specimen collections from several countries of Southeast Asia, utilizing the NCI/LOC. Through such a contract collection, which involved a team of botanists from the U.S. and source countries, samples of *Calophyllum lanigerum*, a tree in a tropical rain forest of Sarawak, Malaysia (locally referred to as bintangor trees), were brought to NCI in 1987 for testing and found to possess significant *in vitro* anti-HIV activity. Isolation and characterization of the active components at NCI and pre-clinical development with the assistance of an industrial partner, Medichem Research, Inc., led to the discovery of two anti-HIV agents belonging to the coumarin class of compounds - calanolides A and B - currently in Phase I/II clinical trials [1, 13, and references therein].

Drug Discovery and Development

About 90,000 extracts obtained from natural products, were screened at NCI between 1988 and 1996, through its DTP. Among these, the organic extracts from twigs and leaves of the tree *Calophyllum lanigerum*, collected in Sarawak, Malaysia in 1987, showed significant *in vitro* anti-HIV activity in NCI laboratory screens in 1988. Bioassay-

guided fractionation of the extract yielded (+)-calanolide A as the main *in vitro* active agent. Attempted recollections in Sarawak in 1991 failed to locate the original tree, and collections of other specimens of the same species gave only trace amounts of calanolide A. In 1992, a detailed survey of *C. lanigerum* and related species was undertaken by UIC and botanists of the Sarawak Forestry Department. As part of the survey, latex samples collected from *Calophyllum teysmannii* also yielded extracts with significant anti-HIV activity. The active constituent was found to be (-)-calanolide B, which was isolated in yields of 20 to 30%. While (-)-calanolide B obtained from the latex of *C. teysmannii* is slightly less active than (+)-calanolide A obtained from the twigs of *C. lanigerum*, it has the advantage of being readily available from the latex which is tapped in a sustainable manner by making small slash wounds in the bark of mature trees without causing any harm to the trees. Following the signing of an agreement with the Sarawak State Government (June 1994), NCI proceeded to collect large quantities of the latex for pre-clinical development of both calanolides, for which it obtained patents in 1995. Through an exclusive license from NCI-NIH for the patented compounds, Medichem Research, Inc., a small pharmaceutical company based near Chicago, developed a synthesis of (+)-calanolide A. The development was possible under a Small Business Innovative Research (SBIR) grant from NIH [24]. The company also entered into an agreement with the Sarawak State Government to use the source country as its first supplier, as stipulated by the LOC. By late 1995, the Sarawak State Forestry Department, UIC, and the NCI had collaborated in the collection of over 50 kg of latex of *C. teysmannii*, and kilogram quantities of (-)-calanolide B had been isolated for further development towards clinical trials. Medichem Research advanced the pre-clinical development of (+)-calanolide A, and was granted an INDA for clinical studies by the U. S. Food and Drug Administration (FDA). The company benefited from the research knowledge and expertise of NCI scientists by becoming a collaborator of NCI through the signing of a CRADA for additional preclinical development. Calanolide A, the lead development product of Sarawak-Medichem Pharmaceuticals (SMP, formed by the partnership between Medichem Research and Sarawak State Government) has completed Phase I clinical trials. These clinical studies with healthy volunteers (1996) showed that doses exceeding the expected levels required for efficacy against HIV-1 are well tolerated. Calanolide B is also currently under preclinical development at SMP.

Benefit-Sharing Mechanisms

Benefit sharing was based on the model described earlier in the context of the NCI LOC regarding partnership between NCI and host-country institutions through permits from necessary government authorities. An agreement was signed in June of 1994 between the Sarawak State Government and the NCI for the mass collection of latex from a related species *Calophyllum teysmannii*, for the pre-clinical development of calanolides A and B. In 1995, NCI obtained patents on both calanolides and granted an exclusive license for their clinical development to its industrial partner Medichem Research. As stipulated in the

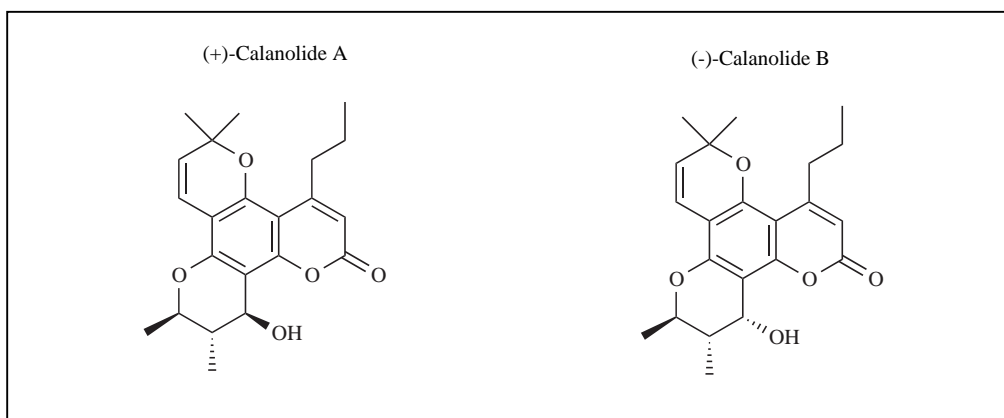


Fig. (1). Chemical structures of Calanolides A and B.

LOC, the licensing agreement between NCI and Medichem Research specified that Medichem Research negotiate an agreement with the Sarawak State Government. In late 1996, the Sarawak State Government and Medichem Research formed a joint venture company, Sarawak Medichem Pharmaceuticals Incorporated (SMP), which has sponsored Phase I clinical studies with healthy volunteers.

Future Goals

Calanolides A and B are new, diastereomeric, non-nucleoside reverse transcriptase inhibitors (NNRTI). Both drugs, which are now being developed by SMP, hold much promise.

The development of the calanolides provides an example of collaboration between a source country (Sarawak, Malaysia), a company (Medichem Research, Inc.) and the NCI in the development of promising drug candidates, and illustrates the effectiveness and strong commitment of the NCI to policies promoting the rights of source countries to fair and equitable compensation in the drug discovery and development process. This success story has been showcased as a "Benefit-Sharing Case Study" for the Executive Secretary of the Convention on Biological Diversity by staff of the Royal Botanic Gardens, Kew [25].

2. ANTI-CANCER DRUG CANDIDATE HTI-286 – SYNTHETIC ANALOGUE OF TRIPEPTIDE OBTAINED FROM MARINE SPONGE

NIH Program

NCI/NCDDG - Anticancer Agents from Unique Natural Products Sources

Consortium Goal

To discover and develop novel anticancer agents from organisms inhabiting unique ecological niches.

Consortium Members

U.S. Academic Partner(s) – University of Utah (UU), Harvard Medical School (HMS)

U.S. Industrial Partner(s) – Wyeth Research: Oncology Research Group

International Partner(s) – University of British Columbia (UBC), University of Papua New Guinea (UPNG),

University of the Philippines; University of South Pacific, Fiji Islands; Colombo University, Sri Lanka; Instituto de Quimica de Sao Carlos, and Universidade de Sao Paulo, Brazil.

Genetic Resources utilized – organisms from unique habitats e.g., marine sponges

Traditional Knowledge utilized – None

In 1995 a consortium comprised of the above academic and industrial partners formed a National Cooperative Natural Products Drug Discovery Group (NCNPDDG) through the NCI NCDDG Program to explore organisms from unique environmental niches for the purpose of discovering agents with anti-cancer properties. The group chose to explore unusual habitats based on the rationale that chemical diversity occurs concurrently with biological diversity, which is specifically enriched under selection pressure in unique environments. Dr. M. Ireland from the University of Utah, who served as the principal investigator of this group, coordinated the activities of the associate programs (operated from other academic centers and the industry) and also communicated with the NCI/NCDDG representatives. The industrial partner Wyeth Research served as an integral member of the group for investigating the chemistry of marine microorganisms through high-throughput automated screening systems, pre-clinical and clinical developmental studies. The initial phase of discovery of the hemiasterlin tripeptides began prior to the NCDDG partnership involving several other academic and corporate collaborations, such as between UBC, UPNG and the University of Alberta, and between UBC and the Lederle Laboratories of American Cyanamid (now Wyeth). Detailed history of the discovery and development of the synthetic hemiasterlin analogue HTI-286 is provided in reference 26 (and references therein), of which only the key events are highlighted below.

Drug Discovery and Development

The UBC, UPNG and Wyeth team (coordinated through UU) screened natural products from marine invertebrates such as sponges for anti-cancer drug potential. This led to the isolation of a variety of complex compounds. Particularly of interest was the activity isolated from crude extract of *Cymbastella* sp., which had identical optical properties to the

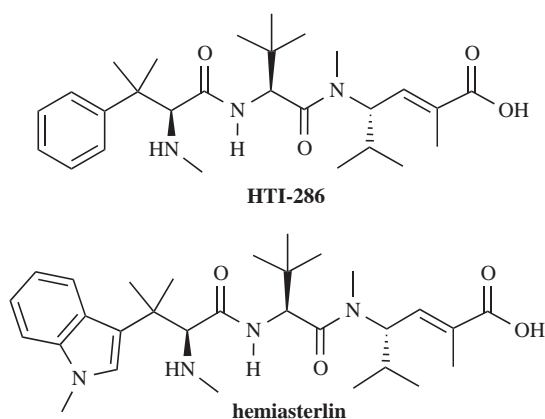


Fig. (2). Chemical structures of hemiasterlin and its analog HTI-286. [Reprinted from Loganzo F. *et al.* (2003) *Cancer Research* 63, 1838-1845].

tripeptide hemiasterlin, first reported from the South African sponge *Hemiasterella minor* and subsequently from other sponge species. Unlike the South African sponges, the PNG specimens yielded sufficient quantities of the tripeptide for structural and biological analyses. The hemiasterlin from *Cymbastella sp.* was found to be thousand-fold more potent than that originally isolated from *H. minor* in *in vivo* cytotoxicity tests. Further research revealed that hemiasterlin inhibits mitosis and binds at the vinca/peptide region of tubulin, which is a target for a wide variety of structurally complex natural products. However, because the sponge extract also contained other compounds such as jaspamides and geodiamolodes, refined biochemical analyses were necessary to rule out the role of these impurities. The UBC team found a method to synthesize hemiasterlin analogs in large quantities in the lab, devoid of impurities, and partnered with Wyeth for their further development and biological evaluation. The biological profile of one such analogue, HTI-286, showed that it inhibited the polymerization of purified tubulin, disrupted microtubule organization in cells, and induced mitotic arrest, as well as apoptosis. Scientists at Wyeth studied the structure-activity relationships (SAR) for the drug's binding to tubulin, evaluated the potency and efficacy of the analog in cell lines resistant to the anticancer drug paclitaxel and sought to elucidate the mechanisms of HTI-286 resistance, if any. Resistance to HTI-286 was not detected in cells overexpressing specific drug transporters. The Wyeth group found that both *in vitro* and *in vivo*, HTI-286 circumvents P-glycoprotein-mediated resistance common to other anti-microtubule agents such as paclitaxel, vincristine and vinblastine [27]. Moreover, HTI-286 inhibits the growth of numerous human tumors (derived from skin carcinoma) in mice and causes marked regression of established tumors. Undoubtedly, this synthetic chemical derived from the study of natural products holds much promise as it goes into clinical trials for anticancer drug discovery.

Benefit-Sharing Mechanisms

Collaborating partnerships between various programs within the NCNPDDG was established through structured agreements that outlined benefit-sharing mechanisms

compliant with the principles of the UN CBD. For example, in 1995, UU and the University of the Philippines Marine Science Institute (UP-MSI) executed an MOU specifying co-ownership of patents and equal sharing of revenues from IP generated in collaborative research performed at both institutions. The agreement also included terms of technology transfer and training opportunities for Filipino students and scientists, and provided an independent budget from NCDDG to UP-MSI for laboratory research and scientific infrastructure. Furthermore, following the implementation of new regulations in the Philippines in 1997, commercial research agreements (CRAs) needed for sample collection, were signed according to mandate. The partnership between UBC, UPNG and Wyeth Research, which led to the development of the anticancer drug candidate HTI-286, was also established through similar agreements with source country-specific budget allocations. A license agreement signed between UBC and Wyeth for this purpose enabled a steady flow of milestone royalty payments to UPNG and Papua New Guinea's Biodiversity and Conservation authority PNG-BioNet.

Future Goals

Subsequent to the above discovery, UPNG, UU and NIH have become partners through the ICBG program to search for marine organisms and plant species that may contain future remedies against tuberculosis, malaria, cancer, HIV and other diseases.

3. THE CASE OF THE LATENT HIV ACTIVATOR PROSTRATIN – TRADITIONAL KNOWLEDGE AND GENETIC RESOURCES OF WESTERN SAMOA

NIH Program

NCI/DTP; FIC/ICBG

Consortium Goal

Anti-HIV drug discovery

Consortium Members

U.S. Academic Partner(s) – Brigham Young University, Utah; University of California at Berkeley (UCB)

U.S. Commercialization Partner – AIDS Research Alliance of America (ARA)

International Partner(s) – Government of Western Samoa

Genetic Resources utilized – *Homalanthus nutans*, known as the Mamala tree in Samoa

Traditional Knowledge utilized – The plant has been used by Samoan traditional healers for treatment of liver diseases, the symptoms of which resembled those of yellow fever and hepatitis.

In 1984 Dr. Paul Alan Cox, then at Brigham Young University in Utah (currently Director of the National Tropical Botanical Garden, Hawaii), initiated the study of Samoan medicinal plants in collaboration with traditional healers from the village of Falealupo in Western Samoa. Based on his interviews Dr. Cox learned about the Mamala tree (*Homalanthus nutans*) as being used by the locals for the

treatment of liver disease resembling yellow fever, subsequently identified as hepatitis. Further research on this tree by Cox and collaborators led to the discovery of prostratin, now a candidate drug for eradication of residual latent HIV infection from T cells in patients undergoing highly active anti-retroviral therapy (HAART) [13 and references therein, 28].

Drug Discovery and Development

In 1989, Cox submitted an extract of the wood of *H. nutans* for *in vitro* anticancer and anti-HIV testing at NCI. The extract showed significant anti-HIV activity in a cell-based screen. Bioassay-guided fractionation of the extract by NCI chemists yielded prostratin, a 12-deoxyphorbol. NCI workers found that, unlike other phorbol esters, prostratin is not a tumor-promoter. Furthermore, studies by a group at the AIDS Institute, University of California at Los Angeles (UCLA) showed that prostratin was a potent activator of HIV expression in latently infected T-cell lines [29]. While this surprising discovery initially ruled out prostratin as an anti-HIV drug, it was soon realized that the utility of prostratin as a viral activator could be of immense value in HIV therapy. The agent could be potentially used for flushing out latent HIV from lymph nodes; the virus could then be eradicated with HAART. Currently, the partnership with ARA - a community-based non-profit research organization that is fighting AIDS on multiple fronts, and collaborating with laboratories around the world - is expected to promote further research and development of prostratin. ARA is helping to sponsor clinical trials of prostratin.

Benefit-Sharing Mechanisms

In his research, both the genetic resources as well as traditional knowledge of Samoa were utilized. Dr. Cox negotiated an agreement with the chiefs and orators in the village of Falealupo, with the concurrence of the Samoan Prime Minister and members of parliament (1). Under this agreement, over \$480,000 have been supplied to the village for development of schools, medical clinics, water supplies, trails, an aerial rain forest canopy walkway, and also to establish an endowment for the rain forest.

After the therapeutic potential of prostratin (derived from a Samoan medicinal tree) became known from drug screens conducted at NCI, a licensing agreement was signed between NIH and ARA in 2001 for further study and development of prostratin. As required by the NCI LOC, ARA has negotiated an agreement with the government of Samoa. The agreement signed by the Samoan Prime Minister, allows for benchmark payments to the government of Samoa upon execution of the agreement, and upon completion on Phase I, Phase II and Phase III clinical trials. If prostratin is approved for marketing, ARA agrees to share approximately 20% of commercial profits with the Samoans. It will pay the following royalties as percentages of net revenues: 12.5% to the Samoan government; 6.7% to Falealupo village; 0.4% each to the descendants of the two healers associated with the identification and formulation and use of *H. nutans*. Also, ARA will endeavor to (1) obtain prostratin from Samoan plant sources as long as it can be produced in a cost-

effective manner, and will urge any sub-licensee to do likewise; (2) ensure that the drug will be distributed at minimal profit in developing nations where use of the drug is approved.

In 2004, yet another agreement was signed between the Samoan government and UCB for the cloning of prostratin genes from *H. nutans* and its mass production in microbes by genetic engineering. The agreement, signed by the Prime Minister of Samoa and the Vice Chancellor for Research at UCB, gives both parties equal shares to any commercial development from the genetic resource. The 50% share allocated to the Samoan government will be distributed at various levels to the villages and families who initially shared their traditional knowledge with Cox.

Future Goals

Most recently, a team of scientists at UCB led by Dr. Jay Keasling, have geared up to produce prostratin in the laboratory by cloning the corresponding genes from *H. nutans* into the bacterium *Escherichia coli* [30]. It is hoped that by genetic engineering, an abundant supply of the chemical might be obtained for future drug development at a low cost. As stated in their mutual agreement, if the project is successful, Samoa and UCB will negotiate the distribution of the drug in developing nations at a minimal profit.

The recent collaboration between Cox and colleagues of the National Tropical Botanical Garden in Hawaii, the Samoan Ministry of Trade and Tourism, the UCB and the ARA has been made possible in part through an ICBG Planning Grant from NIH/FIC. This collaboration supports all the goals of ICBG in promoting drug discovery, sustainable economic development and conservation of biodiversity in Western Samoa.

The story of prostratin demonstrates a novel approach to drug discovery in which the ancient wisdom of Samoan tradition comes together with modern biomedical technology to find a potential treatment for one of the greatest plagues of the 21st century - HIV/AIDS. It also illustrates a possible

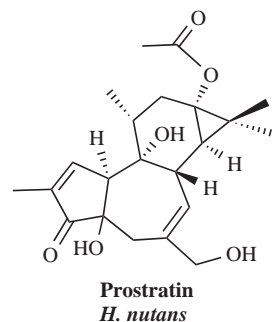


Fig. (3). Chemical structure of Prostratin.

mechanism for entirely different cultures to share the benefits derived from the fruits of their joint endeavor.

DISCUSSION (LOOKING AHEAD WITH THE LESSONS LEARNED)

With the world getting increasingly smaller, we are faced today with greater challenges as well as opportunities. From

a health perspective, emergence of new infectious diseases e.g., SARS or H5N1, and re-emergence of almost eradicated diseases, such as tuberculosis, pose threat to all. Rapid international travel can spread a contagious disease around the globe in a matter of hours. Many infectious diseases have now become resistant to standard therapeutic agents (such as antibiotics), and multi-drug resistance is also common to non-infectious diseases such as certain cancers. Unfortunately, with very few new drugs currently available in the market, there is an increased need to expedite the process of drug discovery and to look for drugs from novel sources. This has stimulated a renewed interest in the hunt for natural products, even by high-tech pharmaceutical companies and research foundations that are armed with latest state-of-the art technologies. For example, exploration in the deep oceans has recently led to the identification of novel compounds from marine organisms [31].

Research on natural products has also become a priority in countries known for their traditional medicine. For example, China and India are making major investments to increase their research and development in the areas of health-care industry that involve natural products (e.g., herbal medicines and beauty products) to satisfy their growing demand in domestic and international markets. With the process of globalization as cultures across nations come together, more westerners are looking for solutions beyond allopathic medicine and using treatments available in ethnic herbal remedies. Hence, western medicine is now turning its attention to traditional medicine and is eager to test herbal and other natural remedies through conventional scientific methods and clinical trials under the category of so called "Alternative Medicine." Indeed, the National Center for Complimentary and Alternative Medicine (NCCAM) at NIH funds research to evaluate traditional medicine and assess the medical importance of certain herbal extracts and compounds.

As further research in these fields proceeds, there are major international efforts to facilitate cooperation on all fronts in the field of drug discovery. International collaboration is essential to share knowledge, expertise and resources for the benefit of global public health. Hence, there are attempts to harmonize the regulatory frameworks for clinical trials, drug development and approval. There are also attempts to harmonize IP regimes, such as through the TRIPS Agreement of WTO, to promote innovation and economic growth, particularly for countries that are technologically advanced and ready for cooperative partnerships. Finally, as discussed earlier, there are mechanisms in place, through international instruments, such as the CBD, to protect and promote the natural assets of countries that are rich in genetic resources so that they can enter into meaningful partnerships with technologically advanced nations for effective utilization of these resources. However, in order to make these instruments work, attention needs to be given to what lessons have been learned in the past and the cumulative wisdom needs to be used for facilitating future cooperation between the resource-rich countries of the south and the technology-rich countries of the north.

Before entering into any major collaboration, it is important that all involved parties understand clearly what they are agreeing to do, the commitments they are willing to make, the expectations of the outcome and the risks involved, if any. Thus, prior to the start of the project, it is important to obtain PIC from all parties concerned, as stipulated by the CBD Article 15.5. As discussed earlier (in the context of ICBG), this can be a daunting task when the authority to give consent is not clearly defined. Lessons can be learned from other areas of research, such as clinical trials performed in other parts of the world in entirely different cultural settings. Scientists and field workers have found that in certain cultures consent must first be obtained from the community or the family head before approaching the immediate individual(s) [32]. Likewise, in the case of traditional knowledge or genetic resources, one may need to obtain permission at various levels and must follow the regulatory/ethical guidelines, no matter how slow the process might be, to avoid misunderstandings and dissolution of project at a late phase. Some have argued that if PIC becomes a mechanism for unnecessary delay, the effort may be counter productive and will adversely affect the technology transfer process in developing countries [33]. Nonetheless, it is a foremost hurdle that needs to be crossed before one proceeds to the next step. Transparency is the key to success and patience is a virtue in such endeavors [11]. Moreover, PIC does not merely mean a signed document. To be effective, all parties must clearly understand the terms to which they give consent; if not, this can pose major problems down the road. The major challenge lies in translating western concepts of ownership, particularly for abstract ideas such as IP, for cultures to which these terms are entirely foreign and which do not have comparable vocabulary.

A second issue of importance is valuation of genetic resources and traditional knowledge. Many conservationists have emphasized that the incentive of the indigenous peoples to conserve their natural resources of medical and economic importance can only come from their understanding of the appropriate value and possible ownership of these resources [34]. If not, valuable biomaterials, in the tropical rainforests for example, may be lost before scientists have a chance to study them for drug discovery. However, it remains debatable as to what kind of value should be reasonable for indigenous people to put on their genetic resources and traditional knowledge. In world forums related to trade and IP, the source countries may try to correlate the long-term value of their natural resources with royalties from blockbuster drugs instead of also taking into account other forms of benefits. But as the history of drug research shows, the chance of making such breakthrough drug discoveries are few and far between and can take up to 10-15 years. This is the case with 8 ICBG programs, which have not yielded any pharmaceutical products, even after more than 10 years of work [36]. Hence, valuation should not be based on unrealistic expectations but rather should take into account the "economic realities" encountered in drug discovery and development. Therefore, benefit sharing agreements, involving bio-prospecting, should also focus on short-term tangible benefits to the source countries with relation to public health [11]. Such benefits include development of

technology and infrastructure, training of research scientists and technicians so that eventually they may be capable of developing and manufacturing these products from natural resources within their home countries [34]. Hence, in 2-3 decades, which may yield only a handful of drugs, one can build up an entire generation of skilled workforce for independent research and development. Such trainees can become long-term partners for collaboration and the future of a nation's knowledge-based economic development. Moreover, such a generation would be more cognizant of the value of their resources and more realistic in their expectations. To that end, some have argued that in return for resources and traditional knowledge, cooperative agreements should emphasize legal assistance or the capacity building of source countries in legal aspects of IP protection and technology transfer [35].

In recent years, several countries (such as China, India and Venezuela) have taken the initiative to document their traditional knowledge and associated natural resources in national public databases (TK-databases) that may be accessed by major patent offices (such as USPTO, EPO, etc.) around the world [36]. Similar TK-databases have also been set up by certain international organizations, universities, etc., such as the Portal of Online Databases and Registries of Traditional Knowledge and Genetic Resources established by the World Intellectual Property Organization (WIPO) and the NATural PROducts ALERT (NAPRALERT) of the University of Illinois at Chicago (UIC/NIH Center for Botanical Dietary Supplement Research in Women's Health) [37, 38]. It is anticipated that use of such databases by patent examiners for search of "prior art" may prevent erroneous patenting (and unnecessary expensive law suits attempting to revoke those issued patents) of plant materials that have long been traditionally used in their native lands for their medicinal properties. This is yet another method of valuation of traditional knowledge and indigenous genetic resources.

All of the above elements - PIC, capacity building and valuation of traditional knowledge and genetic resources - have been addressed in the various NIH programs that were discussed in this paper in the context of natural products and drug discovery. Various drug discovery programs at NIH have made significant advances in new approaches to these complex issues. While not uniformly administered across NIH, the basic concepts have been widely adapted, and for instance now appear explicitly in strategic plans and programs in other components of NIH and other agencies of the U.S. Government. Hence the cumulative knowledge and experience acquired over almost 20 years at NIH in the field of natural products and drug discovery may be of use to those international groups seeking to develop their own models of cooperation for the benefit of global health.

LIST OF ACRONYMS USED IN THIS ARTICLE

TK	=	Traditional Knowledge
IP	=	Intellectual Property
IPR	=	Intellectual Property Rights
TRIPS	=	Trade Related Aspects of Intellectual Property Rights

WIPO	=	World Intellectual Property Organization
WTO	=	World Trade Organization
CBD	=	Convention on Biological Diversity
SC	=	Source Country
SCO	=	Source Country Organization
SCG	=	Source Country Government
USG	=	U.S. Government
NGO	=	Non-Governmental Organization
NIH	=	National Institutes of Health
NCI	=	National Cancer Institute
FIC	=	Fogarty International Center
DCTD	=	Division of Cancer Treatment & Diagnosis
CTEP	=	Clinical Trials Evaluation Program
NPB	=	Natural Products Branch
NPR	=	Natural Products Repository
HTS	=	High-Throughput Screening
DTP	=	Developmental Therapeutics Program
NCDDG	=	National Cooperative Drug Discovery Group
NCNPDDG	=	National Cooperative Natural Products Drug Discovery Group
ICBG	=	International Cooperative Biodiversity Group
LOC	=	Letter of Collection
MOU	=	Memorandum of Understanding
MTA	=	Material Transfer Agreement
CRADA	=	Cooperative Research And Development Agreement
FDA	=	Food & Drug Administration
INDA	=	Investigational New Drug Application
NDA	=	New Drug Application
RFA	=	Request for Applications

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